PROF. ASLI GELINCIK (Orcid ID : 0000-0002-3524-9952)

PROF. KNUT BROCKOW (Orcid ID : 0000-0002-2775-3681)

PROF. GULFEM ELIF CELIK (Orcid ID : 0000-0001-8654-513X)

DR. INMACULADA DOÑA (Orcid ID : 0000-0002-5309-4878)

DR. CRISTOBALINA MAYORGA (Orcid ID : 0000-0001-8852-8077)

PROF. MARINA ATANASKOVIĆ-MARKOVIĆ (Orcid ID : 0000-0003-1354-6072)

Article type : Review

Corresponding author mail id : gelincikasli@hotmail.com

Title page

Diagnosis and management of the drug hypersensitivity reactions in Coronavirus disease 19

Running head: Drug hypersensitivity reactions in COVID-19

Aslı Gelincik[1], Knut Brockow[2], Gülfem E Çelik[3], Inmaculada Doña[4,5], Lina Mayorga[6], Antonino Romano[7], Özge Soyer[8],Marina Atanaskovic-Markovic[9], Annick Barbaud[10,11], Maria Jose Torres[12]

1. Department of Internal Medicine, Division of Immunology and Allergic Diseases, Istanbul Faculty of Medicine, Istanbul University, Istanbul, Turkey

2. Department of Dermatology and Allergy Biederstein, Faculty of Medicine, Technical University of Munich, Munich, Germany

3. Department of Chest Diseases, Division of Immunology and Allergy, Ankara University School of Medicine, Ankara, Turkey

4. Allergy Unit, Hospital Regional Universitario de Málaga-ARADyAL. Málaga, Spain.

5. Allergy Research Group, Instituto de Investigación Biomédica de Málaga-IBIMA-ARADyAL. Málaga, Spain.

6. Research Laboratory, IBIMA-Regional University Hospital of Malaga-UMA-ARADyAL, Malaga, Spain.

7. IRCCS Oasi Maria S.S., Troina, Italy & Fondazione Mediterranea G.B. Morgagni, Catania, Italy.

8. Hacettepe University School of Medicine, Pediatric allergy department, Ankara, Turkey.

9. Faculty of Medicine, University of Belgrade, University Children's Hospital, Belgrade, Serbia.

10. Sorbonne Université, AP-HP.Sorbonne Université, Hôpital Tenon, Département de dermatologie et allergologie, F75020, Paris, France.

11. Institut Pierre Louis d'Epidémiologie et de Santé Publique, AP-HP. Sorbonne Université, Paris, France.

12. Allergy Unit, Regional University Hospital of Malaga-IBIMA-UMA-BIONAND-ARADyAL, Malaga, Spain.

Corresponding author:

Aslı Gelincik MD, Prof Dr

Department of Internal Medicine, Division of Immunology and Allergic DiseasesIstanbul University, Istanbul Faculty of Medicine, Turgut Özal Millet Cad, 34390, Fatih, Istanbul

Phone: +905422370665

Word count:5114

Conflict of Interest statement: None of the authors declare conflict of interest.

Author contributions:

Aslı Gelincik has made substantial contributions to conception and design, or acquisition of data, or analysis and interpretation of data; has been involved in drafting the manuscript or revising it critically for important intellectual content.

Knut Brockow has made substantial contributions to conception and design, or acquisition of data, or analysis and interpretation of data; has been involved in drafting the manuscript or revising it critically for important intellectual content.

Gülfem E Çelik has made substantial contributions to conception and design, or acquisition of data, or analysis and interpretation of data; has been involved in drafting the manuscript or revising it critically for important intellectual content.

Inmaculada Doña has made substantial contributions to conception and design, or acquisition of data, or analysis and interpretation of data; has been involved in drafting the manuscript or revising it critically for important intellectual content.

Lina Mayorga has made substantial contributions to conception and design, or acquisition of data, or analysis and interpretation of data; has been involved in drafting the manuscript or revising it critically for important intellectual content.

Antonino Romano has made substantial contributions to conception and design, or acquisition of data, or analysis and interpretation of data; has been involved in drafting the manuscript or revising it critically for important intellectual content.

Özge Soyer has made substantial contributions to conception and design, or acquisition of data, or analysis and interpretation of data; has been involved in drafting the manuscript or revising it critically for important intellectual content.

Marina Atanaskovic-Markovic has made substantial contributions to conception and design, or acquisition of data, or analysis and interpretation of data; has been involved in drafting the manuscript or revising it critically for important intellectual content.

Annick Barbaud has made substantial contributions to conception and design, or acquisition of data, or analysis and interpretation of data; has been involved in drafting the manuscript or revising it critically for important intellectual content.

Maria Jose Torres has made substantial contributions to conception and design, or acquisition of data, or analysis and interpretation of data; has been involved in drafting the manuscript or revising it critically for important intellectual content.

Abstract

Coronavirus disease 2019 (COVID-19), a respiratory tract infection caused by a novel human coronavirus, the severe acute respiratory syndrome coronavirus 2, leads to a wide spectrum of clinical manifestations ranging from asymptomatic cases to patients with mild and severe symptoms, with or without pneumonia. Given the huge influence caused by the overwhelming COVID-19 pandemic affecting over three million people worldwide, a wide spectrum of drugs is considered for the treatment in the concept of repurposing and off-label use. There is no knowledge about the diagnosis and clinical management of the drug hypersensitivity reactions that can potentially occur during the disease. This review brings togetherall the published information about the diagnosis and management of drug hypersensitivity reactions due to current and candidate off-label drugs andhighlights relevant recommendations. Furthermore, it gathers all the dermatologic manifestations reported during the disease for guiding the clinicians

to establish a better differential diagnosis of drug hypersensitivity reactionsin the course of the disease.

Key words: COVID-19, desensitization, drug hypersensitivity reactions, SARS-CoV2

INTRODUCTION

Coronavirus disease 2019 (COVID-19) is a respiratory tract infection caused by a novel member of human coronavirus, the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)(1). It causes a wide spectrum of clinical manifestations ranging from asymptomatic cases to patients with mild, uncomplicated illness and severe cases, with or without pneumonia (2). Hospitalization and oxygen support, and admission to an intensive care unit are required in 14% and 5% of the patients, respectively (1). Gastrointestinal symptoms and positive viral nucleic acid testing on rectal swabs are considered as indicators of infection in digestive system and fecal-oral transmission of COVID-19(3). Moreover, skin symptoms, including exanthems, may appear during the evolution of the disease leading to differential diagnosis with drug hypersensitivity reactions (DHRs)(4).

In critically ill patients, COVID-19 can be complicated by acute respiratory distress syndrome (ARDS), septic shock, and multi-organ dysfunction syndrome (1). In such patients, in response to viral infection, the excessive activation and expansion of T lymphocytes and macrophages lead to an overproduction of cytokines, which causes a cytokine storm and a hyperinflammatory state (5, 6). Acute hyperinflammation may activate coagulation cascade and inhibit fibrinolytic reaction, thus promoting thrombosis. Coagulopathy and thrombocytopenia are serious complications which increase the risk of haemorrhage and thrombosis and progress to disseminated intravascular coagulation (DIC)(7).

The periodically updated World Health Organisation interim guidance allows reliable comparison of investigational therapeutic interventions as part of randomized controlled trials, provides recommendations for the management and forms the basis of many institutional or national protocols (1). Unfortunately, none of the drugs used for COVID-19 have been proven to be truly effectiveyet; besides, no specific antiviral drugs have been approved for COVID-19 by health authorities(8,9). At the moment, there is no specific treatment for COVID-19, and standard practice of care focuses on treating the clinical symptoms with supportive care (1).

In this review, diagnosis and management of DHRs, which are expected to be caused by current or candidate repurposed and off-label drugsusedfor COVID-19treatment mostly based on prior knowledge,are discussed (8,10,11). Drugs in this review are classified into four groups according to their potential roles in different phases of the disease asantiviral drugs, antiviral and/or immunomodulatory drugs used in viral pneumonia; anti-cytokine and anti-inflammatory drugs considered during macrophage activation syndrome (MAS) and cytokine storm; anti-inflammatory drugs in ARDS; and anti-aggregant and anti-coagulant drugs in coagulopathy (Figure 1). Information of DHRs due to the use of additional drugs for various purposes can be found in the relevant European Academy of Allergy and Clinical Immunology (EAACI) resources (12-20).

Since emerging recent findings are dynamically changing the clinical interventions, it is expected that the list of drugs determined according to current knowledge may change with upcoming recommendations in future.

SKIN MANIFESTATIONS INDUCED BY COVID-19

There have been increasing reports of dermatologic manifestations associated with COVID-19(Table 1).It is knowledge, although in progress, rapidly evolving as evidenced by most publications being ahead of print and available only in an electronic version or reported in networks.

According to pathogenetic mechanisms, skin manifestations reported so far can be divided into 1. Skin manifestations similar to those in other viral infections, and 2. Skin manifestations related to thrombovascular events and vascular pathologies.

1. Skin manifestations similar to those in other viral infections

During the COVID-19 outbreak in China, it was not a focus to document skin manifestations. Consequently, skin rash has only been reported in 2 out of 1.099 infected patients (0.2%)(21).In contrast, a study by dermatologists from Italy reported skin manifestations in 18/88 patients (20.4%) with COVID-19(4). Cutaneous manifestations seen were either erythematous rash (n=14), widespread urticaria (n=3), or chickenpox-like vesicular rash (n=1).In Spain, among 375 patients with suspected or confirmed COVID-19, maculopapular eruptions (MPEs), sometimes similar to pityriasis rosea, were observed in 47% of the cases, urticarial lesions in 19% and vesicular eruptions of the trunk in 9% (22).Another case of urticaria was presented in France (Figure2A)(23) and patients with morbilliform exanthem in the USA(Figure 2B)(24). Varicella-like lesions predominantly on the trunk were described in 22 patients with proven COVID-19infection in Italy(25). Predominance of vesicles was reported in 54.5% and generally mild itching in nine (40.9%) patients. The vesiculopapular exanthem appears to develop early in the course of the disease (Figure 2C(26))(22,26).An outbreak of severe Kawasaki-like disease has been reported at epicentres of Covid-19 infection also associated with a polymorphic rash in 30-50% of affected children (27,28). In one case, picture of a urticaria-like rash in a 6-month old child with Kawasaki-like disease associated with Covid-19 infection is shown (Figure 1S) (29).Two patients with bilateral flexural exanthems resembling systemic drug-related intertriginous exanthems (SDRIFE), one with axillary purpuric lesions associated with thrombocytopenia, have been published (Figure 2D) (30).A prospective study from France reported a prevalence of 5/103 (4.9%) and confirmed association of pruritic erythematous rash (n=2) and urticaria (n=2) with COVID-19infections (31); they additionally observed oneoral herpes simplex virus type 1 reactivation. The histopathological picture of exanthematic skin lesions generally resembles that of viral exanthems. However, in individual patients, early microthrombi and an interface dermatitis with necrotic keratinocytes surrounded by lymphocytes have been reported (32).

2. Skin manifestations associated with thrombovascular events and vascular pathologies

COVID-19exanthems have also been reported with petechiae and low platelet count resembling dengue (33).In two patients, unilateral lesions on the thigh resembling *livedo reticularis* or erythema *ab igne* have been described with microthromboses discussed as possible etiology (Figure 3A) (34).

Chilblain-like skin lesions have been frequently reported to be associated with COVID-19(22,35,36,37) (Figure 3B(35)). They appear in up to 19% of patients, typically in mildly affected ones, and late in the evolution of the disease (22,37). Vesicles, pustules and erosions on these violaceous plaques may occur (37). In Spain they were observed in 19% of 375 cases (22).

Seven patients had cutaneous acro-ischemia including finger and toe cyanosis, skin bulla and dry gangrene associated with COVID-19 infection-induced hypercoagulation including definitive DIC in four patients. Five of these patients finally died(Figure 3C)(38). A catastrophic microvascular injury syndrome mediated by activation of complement pathways and an associated procoagulant state were described in severe COVID-19 with purpuric skin rash in 3/5 patients(39).

In conclusion, the prevalence of cutaneous manifestations in COVID-19 patients has been reported between 0.2%, 4.9% and 20.9% (4,21,30).Most skin manifestations resemble cutaneous involvement commonly occurring during viral infections, i.e. erythematous rash and acute urticaria. Drug exanthems have to be considered as differential diagnosis(15). Vesicular varicella-like exanthems may be more specific for COVID-19.Flexural distribution, and petechia as well as erythema ab igne-like lesions have been described. Violaceous, infiltrated painful plaques resembling chilblains have been frequently reported and discussed as typical manifestations. Necrotic lesions occurred in older and in severely ill patients with increased mortality (22).Cutaneous acro-ischemic microthromboses and small blood vessel occlusion have to be further explored for their causality and specificity for COVID-19 manifestations.

ANTI-VIRAL AGENTS USED FOR VIRAL PNEUMONIA

Clinical usein COVID-19

Mostantiviral agents used for COVID-19act either by inhibiting RNA-dependent RNA polymerase [remdesivir (GS-5734)] or proteases [lopinavir/ritonavir (LPV/r), favipiravir (FPV), ribavirin and darunavir] (40-43). Additionally, umifenovir plays a role in viral entry by inhibiting the hemagglutinin-mediated membrane fusion, and oseltamivir is a neuraminidase inhibitor which blocks the release of viral particles from the host cells in influenza infection (44).Remdesivir and FPV are considered to be the most effective agents and are mostly used in combination with

other COVID-19 medications likehydroxychloroquine(40-43). Oseltamivir is recommended for concomitant influenza infection (45). Darunavir or LPV/rcan be concomitantly administered with chloroquine orhydroxychloroquine(43).

Hypersensitivity reactions

DHRs to ribavirin,darunavir, LPV/r, remdesivir,and oseltamivir are rarely reported whereas no DHRs to favipiravir and umifenovirare known at present (46-51) (Table 2).

Ribavirin

Ribavirin is used in combination with pegylated-interferon α2a (peg-IFN-α2a)for treating chronic hepatitis C, and both have been associated with several cutaneous DHRs(52). Ribavirin alone causesdermatitis, alopecia, and photoallergic eczematous reactions (53,54), and the risk of DHR increases with combination therapy: rash [response rate (RR),1.74; 95% confidence interval (CI), 1.17-2.6], dermatitis (RR, 1.67; 95% CI, 1.21-2.30), and pruritus (RR, 1.62; 95% CI,1.29-2.02) (55). A meta-analysis revealed that, on combination therapy, mild to moderate cutaneous reactions appear in 13.3% ofpatients, localized cutaneous reactions in2.6%, generalized reactions-pruritus, skin xerosis and eczematous changes in 10.3%, alopecia in 4.1%, and exacerbation of lichen planus in less than 1%(46)(Table 2).

The etiological diagnosisis difficultin case of combination therapy. A drug provocation test (DPT) confirmed the diagnosis of ribavirin hypersensitivity in a patient having MPE due to combined use of peg-IFN-α2a and ribavirin(56).In another case, an erythema multiforme type drug eruption occurredwith peg-IFN-α2a, ribavirin and/or fluvastatin sodium therapy and a positive lymphocyte transformation test (LTT) confirmed the diagnosis of ribavirin hypersensitivity (57). Successful desensitization protocolswere reported (58,59)(Table 2).

Lopinavir/ritonavir (LPV/r)

LPV/r, either alone or in combination, has been rarely reported to be associated with DHRs.In human immunodeficiency virus (HIV) infected patients who received LPV/r combination, MPE rate was reported as 2-4% (60). Acute Generalized Exanthematous Pustulosis (AGEP) was described in two cases receiving LPV/r(61)(Table 2).

In a multicentre randomized study that evaluated the long-term efficacy and safety of the combination of efavirenz or LPV/r plus abacavir/lamivudine, 2/63 patients in the LPV/r group discontinued the study because of a DHR(62).

In a recent cohort of 199 severe COVID-19 patients who received LPV/r combination, only two (1%) experienced self-limited skin eruptions (47). A recent study evaluating 217 patients from China revealed that most of the adverse drug reactions (ADRs) were associated with LPV/r and umifenovir with 63.8% and 18.1% respectively andhistory of a drug allergy was higher in these patients (8.5%) comparing with the ones without ADRs (2.2% vs., P<0.044) (63).

Darunavir

Darunavir can induce a variety of delayed skin eruptions from mild MPE in most cases, to severe bullous cutaneous reactions in HIV infected patients (48, 64). A phase III randomizedclinical trial performed in 604 patients treated with darunavir/r or LPV/r showed that the percentage of patients experiencing rashwas higher in those receiving darunavir/r compared with others (16% vs 7%). Two patients receiving darunavir/rrequired treatment cessation due to a severerash (48). Darunavir contains a sulfonamide moiety and should be used with caution in patients with a known sulfonamide allergy (65).Desensitization was reported to be successful in patients with non-immediate hypersensitivity reactions (NIHRs) todarunavir(66,67)(Table 2).

Oseltamivir

Oseltamivir, used in influenza,causes rare hypersensitivity reactions although close monitoring of patients is important as 2 cases with Stevens-Johnson syndrome (SJS)/Toxic epidermal necrolysis (TEN) have been reported(49,50), with only one being confirmed by LTT (50).Another case report revealed anaphylaxis due to oseltamivir confirmed by a skin prick test (SPT)(68)(Table 2).

Remdesivir

A recent multicentre study showed that only one (1.6%)out of 61 patientswith COVID-19,experienced MPE during remdesivir treatment and therefore discontinued it prematurely(51)(Table 2).

ANTIVIRAL AND/OR IMMUNOMODULATORY DRUGS USED FOR VIRAL PNEUMONIA

Azithromycin

Clinical use in COVID-19

Azithromycin interferes with virus internalization process in influenza infection (69)and has shownclinical effects in COVID-19 patients, although its mechanism against SARS-CoV-2remains unclear (70).

Hypersensitivity reactions

Regarding immediate hypersensitivity reactions (IHRs), urticaria is the most frequent manifestation (71);furthermore,anaphylaxis can occur (72). Concerning NIHRs, MPE is described to occur independently (73) or only in presence of a concurrent infection (74). Azithromycin has been implicated in contact dermatitis in occupational (75) and non-occupational settings (76).Cases of fixed drug eruption (FDE) (77), AGEP (78) and Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS)(79),SJS (80,81), leukocytoclastic vasculitis(82), and hypersensitivity myocarditis (83)were reported(Table 2).

Diagnosis is complex as skin testing is not validated, presenting discrepancies in non-irritating dilutions for SPT and intradermal test (IDT)(84,85). For NIHRs, positive responses to patch tests (PTs)were described (75). In addition, no validated *in vitro* tests are available (86). Oral DPT remains as the gold standard for diagnosis(87).A successful desensitization protocol was reported in a case of mast cell activation syndrome(88)(Table 2).

Hydroxychloroquine / Chloroquine

Clinical use in COVID-19

Hydroxychloroquine/chloroquine have*in vitro*antiviral effects against SARS-Cov2 by preventing virus/cell fusion, and immunomodulatory effects by inhibiting production of inflammatory cytokines (89).

Hypersensitivity reactions

Dermatologic ADRsaredifficult to be distinguished as a side effect of or an allergic reaction to these drugs or a flare of the underlying dermatological disease(90,91). The most common manifestation is mild pruritic MPEs within initial 4 weeks of treatment(90). High association with AGEP [OR: 39 (8-191)] was described(92). Cases of DRESS (93,94), pustular DRESS (95), erythema

multiforme (96), bullous erythema (97), SJS/TEN (98-100), photoallergic dermatitis (101), and occupational contact dermatitis (102)have beenreported(Table 2).

PTsare reported to be useful for the diagnosis of NIHRs(96,98,103), confirming a T-cell mediated mechanism. However, in a series of 14 patients with ADRs due to chloroquine/hydroxychloroquine, skin tests (STs) were negative in all cases(90). DPT is useful in non-severe cutaneous ADRs in order to differentiate allergic reactions from dermatological adverse effects since only 30% of the patients reporting cutaneous ADRs reveal a positive DPT (90).Successful desensitization protocols of hydroxychloroquine in MPE were reported (104-107). Recently, a 5-hour desensitization protocol for non-immediate urticaria was successfully administered(108)(Table 2).

Two cases of IHR were reported (109,110)and one was confirmed by SPTs(109), however there are no available data for*in vitro*diagnosis. Ahydroxychloroquine desensitization procedure that enables the turning of positive SPTs into negative was published(109). In a case of anaphylaxis a 7 day-desensitization procedure was successfully performed with premedication (110)(Table 2).

Auranofin

Clinical use in COVID-19

Auranofin is an anti-inflammatory compound that can possibly inhibit the replication of SARS-CoV-2 in cell cultureand reduce the expression of cytokines caused by SARS-CoV-2 and the associated lung damage (111).

Hypersensitivity reactions

There are no reported hypersensitivity reactions due to auranofin.

Interferons

Clinical use in COVID-19

Type I IFNs (IFN-α and IFN-β) can inhibit the replication of both SARS and Middle East respiratory syndrome coronavirus (MERS-CoV) and are recommended in combined therapies with other antiviral agents (112,113).

Hypersensitivity reactions

Cutaneous eruptions induced by IFNs are common, with an incidence of 13-23%(114,115). Localized reactions at injection sites are most frequent at 48 weeks(116).Diffuse skin symptoms

including urticaria, generalized eczema, papules arecommon and mostly treated with symptomatic treatment(114, 117,118). Among 26 patients with non-immediate reactions to IFNs, 12 cases reported generalized eczema, 10 MPE, 3 generalized urticaria and 1 lichenoid eruption (119). Cases of FDEs(120), and subacute cutaneous lupus(121)weredescribed(Table 2).

There are few case reports of immediate urticaria (122,123) and anaphylaxis(124,125).For IHRs to IFN-β, positive STswere reported (122, 124).For NIHRs, PTs have a low value and are not recommended, whereas delayed readingIDTs are useful (119,126). A positive DPTwas reported in a patient experiencing anaphylaxis due to peg-INF-α2awith negative STs(125).Successful desensitization protocols both for IHRs (123) and NIHRs (119,127) due to different IFNs were reported(Table 2).

Ivermectin

Clinical use in COVID-19

Ivermectin is an anti-parasitic drug also shown to have an*in vitro* activity against SARS-CoV-2 by inhibition of viral replication(128).

Hypersensitivity reactions

Rare case reports of multiple FDEs (129), confirmed DRESS by skin biopsy and blood eosinophilia (130), confirmed SJS (131) and TEN (132) by skin biopsy were published(Table 2). No data about STs, *in vitro* tests or DPT are available. In addition, no cases of desensitization were reported.

Nitazoxanide

Clinical use in COVID-19

Nitazoxanide is an antiparasitic agent which also has antiviral activities. Combined with hydroxychloroquine or azithromycin, a synergistic effect has been suggested as hydroxychloroquine and azithromycin inhibit viral entry and fusion, while nitazoxanide upregulates innate immune response to prevent on-going viral replicationin COVID-19 (133).

Hypersensitivity reactions

No DHRs to nitazoxanide are reported.

ANTI-CYTOKINE/ANTI-INFLAMMATORY DRUGS USED FOR MAS/CYTOKINE STORM/ARDS

Tocilizumab

Clinical use in COVID-19

Tocilizumab, an anti-IL-6 receptor humanized monoclonal antibody, is under investigation for treatment of COVID-19 and has shown promising results in cytokine storm (6).

Hypersensitivity reactions

The rate of all ADRs to tocilizumab is reported to be around 8%, among them 0.1-0.7% are DHRs (134). DHRs to tocilizumab are both NIHRs (135,136) and IHRs (137-140)(Table 3). In an adult cohort the incidence of IHRs wasreported as 5.5% (139) whereas in a paediatric cohort it was 13.6% (137).

Regarding NIHRs, cases of non-immediate urticaria(141), DRESS (142,143), SJS (144), and AGEP (145) were reported.Younger age, shorter stature, lighter weight, and increased disease activity in the early period of tocilizumab administration have been identified as risk factors for DHRs (146).

Although not standardized, DPTs, SPTs and IDTs wereused for diagnosis of IHRs in case reports(137,139). Only one study revealed that STs have a low negative predictive value in NIHR(140).Desensitization to tocilizumab in NIHRs was effectively applied in a weekly scheme with premedication in one case (141). Rapid drug desensitization is successfullyand routinely used for IHRs (19,134)(Table 3).

Anakinra

Clinical use in COVID-19

Anakinra, a recombinant IL-1 receptor antagonist, is under investigation for the treatment of cytokine storm seen during COVID-19 (5).

Hypersensitivity reactions

Anakinra causes ADRs in 75% of patients. Many of them are related to injection site reactions within the first weeks of application and can present either as an IHR or NIHR (147,148). Systemic IHRs such as urticaria, angioedema, anaphylaxis (149-151), andNIHRs (152) as infiltrating erythematous skin plaques wererarely reported as single cases.IHRafter a first dose of anakinra was reported in a case possibly due to components that are able to induce a direct mast cell degranulation (151,153)(Table 3).

For evaluating IHRs to anakinra, SPTs, and IDTswere performed with the undiluted drug (150,151). Both for IHRs (149,151) and NIHRs (152), successful desensitization protocols were reported(Table 3).

Sarilumab

Clinical use in COVID-19

Sarilumab, another IL-6 receptor antagonist, is under investigation in a phase II/III clinical trial in patients with severe COVID-19 infection (154).

Hypersensitivity reactions

It is generally a well-tolerated drug; however, it can cause local reactions on injection site. In an open-label study, in 3% of the patients it caused a pruritic generalized rash which did not affect the treatment (155)(Table 3).

Canakinumab

Clinical use in COVID-19

Canakinumab, a high-affinity human anti-IL-1β monoclonal antibody, is considered as a candidate in treatment of severe COVID-19 (156).

Hypersensitivity reactions

This anti-IL-1 agent is normally well tolerated and indicated as an alternative in cases with an anaphylactic reaction to anakinra (138). However, there is a recently reportedcase who developed immediate diffuse urticaria after the tenth canakinumab administration and was prevented from further reactions with cetirizine premedication (137)(Table 3).

Janus kinase (JAK) inhibitors (Baricitinib, Ruxolitinib, Tofacitinib)

Clinical use in COVID-19

JAK-inhibitors are under investigation for their potential role in regulating the overactive signalling in the JAK-STAT pathway seen during cytokine storm in critically ill COVID-19 patients. Baricitinib with its potential to inhibit clathrin-mediated endocytosis and its ability to ameliorate associated chronic inflammation in interferonopathies is expected to show promising results in ongoing clinical trials of COVID-19 (157,158).

Hypersensitivity reactions

Few cases were reported: one with a morbiliform eruption and exfoliative dermatitis due to ruxolitinib (159), anotherone with palmoplantar pustulosis due to baricitinib (160),and cases of acute urticaria (161) and palmoplantar pustulosis (162) due to tofacitinib(Table 3).

Cyclosporine

Clinical use in COVID-19

Cyclosporine A prevents the transcription of genes encoding cytokines like IL-2, inhibits the replication of diverse coronaviruses at non-cytotoxic, low-micromolar concentrations *in vitro* (163).

Hypersensitivity reactions

Rare cases of pruritus, urticaria, angioedema and anaphylaxis were reported (164-166). The possible mechanisms can be both immunologic and non-immunologic, which seems to depend on the administration route and formulation (164). In some cases, DHRs have been attributed to the additives such as Castor oil (165), or Cremophor EL(166). SPTs and IDTs or basophil activation test (BAT) can be used for the diagnosis of cyclosporine- and additive-induced IgE-mediated IHRs(18,164,166)(Table 3).

Colchicine

Clinical use in COVID-19

It is a non-selective inhibitor of NLRP3 inflammasome which is thought to be a major pathophysiologic component of ARDS and/or acute lung injury seen in COVID-19 (167).

Hypersensitivity reactions

Rare cases of anaphylaxis (151), confirmed FDE with DPT (168) and successfully desensitized MPE (169) were reported.For PTs, it is recommendedto dilute colchicine to 1% in petrolatum (170)(Table 3).

Eculizumab

Clinical use in COVID-19

Eculizumab, a humanized anti-C5 monoclonal antibody, is under investigation as a candidate drug to play a role in the thrombotic microvascular injury mediated by complement activation causing lung injury either due to severe pneumonia or ARDS in severe COVID-19 (21,36,171).

Hypersensitivity reactions

IHRs or infusion reactions due to eculizumab are very rare (172,173). A case of anaphylaxis diagnosed with STs was sucessfully desensitized with a rapid protocol (174)(Table 3).

Glucocorticoids

Clinical use in COVID-19

In COVID-19 patients, the use of glucocorticoids (GCs) is rather controversial (175,176). Early-start of GCs could be helpful for patients who have an overly exuberant inflammatory response or are at high risk of developing ARDS, whereas the benefit of GCs as rescue treatment remains doubtful (177).

Hypersensitivity reactions

IHRs to GCs are overall rare and mostly IgE-mediated (178-183). In a review of the literature from 2004-2014, anaphylaxis was the most common manifestation reported (60.8%, 73/120 reactions) followed by urticaria and/or angioedema (26.7%). Methylprednisolone was implicated in 41% of reactions, followed by prednisolone (20%), triamcinolone (14%), and hydrocortisone (10%) (181).

In most subjects with IHRs, it is possible to identify the culprit and safe alternative GCs by performing immediate-reading STs (178-185). In the aforementioned review, 74.1% of 112 STs carried out with GCs suspected of being responsible for reactions were positive (181). In some subjects, positive STs were associated with positive serum specific IgE assays and BATs (181,182)(Table 3).

IHRs to medication components other than the GC itself, such as succinate ester used to enhance the solubility in parenteral preparations, have been described (181,185). Hence, when evaluating a reaction to an esterified GC, it is advisable to include in STs the suspected GC and the same GC without the ester component, or with a different ester.

IHRs to excipients or preservatives in GC preparations, such as lactose, carboxymethylcellulose, polyethylene glycol, and hexylene glycol, have also been reported (181,185). Therefore, testing should be performed with a preservative free GC, in addition to preservative testing *per se* if needed (185)(Table 3). A study proposed a comprehensive diagnostic algorithm to evaluate hypersensitivity reactions to GCs, as well as to their components and preservatives (185). This algorithm included STs with Carmellose® eye drops in subjects who had reacted to carboxymethylcellulose-containing GCs and with cow's milk proteins in those who had reacted to lactose-containing GCs.

In the allergy workup, negative results in STs should be confirmed with DPTs (180-185). DPTs are also recommended to ensure tolerance of alternative preparations (184). Cross-reactivity patterns based on structural characteristics have not been clearly established for IHRs as they have been for allergic contact dermatitis (179). DPTs have shown that patients often tolerate alternative GCs belonging to the same chemical group as the responsible GC (182,183). Desensitization to methylprednisolone has been successfully performed (186,187)(Table 3).

NIHRs following systemic administration of GCs have been more rarely reported than IHRs; most reports concerned isolated cases of eczematous or exanthematous skin eruptions (178,179)(Table 3). Some are systemic contact dermatitis, occurring in patients with previous contact dermatitis to GCs. They can be revealed by a Baboon syndrome, characterized by a buttock erythema associated to a symmetric, flexural erythema (188).

Most patients do not have a previous topical sensitization. In NIHRs, the main feature is MPE, but other clinical aspects can also occur such as annular erythema, erythroderma, SDRIFE, AGEP, FDE, and a few cases of SJS (188(Table 3)).

NIHRs can be T-cell-mediated, and PTs, together with delayed-reading IDTs, are useful tools for evaluating them (17).PTs have to be read at 2, 4 and also 7 days. Even though delayed-reading IDTs are more sensitive than PTs, the sensitivity of the former is limited. Therefore, DPTs are often necessary to diagnose NIHRs. In a study by Padial et al, only 2 of the 38 patients with NIHRs to GCs displayed positive delayed-reading IDTs and PTs to the responsible GCs (i.e., dexamethasone and betamethasone), while 21 of the 32 negative patients who agreed to

undergo DPTs reacted to them, experiencing almost exclusively delayed-appearing urticarial eruptions or MPEs (189)(Table 3).

ANTI-COAGULANT AND ANTI-AGGREGANT DRUGS USED FOR COAGULOPATHY

Heparin and low molecular weight heparins (LMWHs)

Clinical use in COVID-19

Heparin [unfractionated heparin (UFH)] and LMWHs are administered for treatment or prophylaxis of thrombosisand therefore it is used for the coagulopathy observed during COVID-19 (190).

Hypersensitivity reactions

UFH may induce all types of DHRs, mostly type IV and type II(191). Cutaneous NIHRs to subcutaneous heparin occur at the injection site as itchy erythematous or eczematous plaques usually on the 7^{th}-10^{th} day of treatment; although they can appear on the 1-3^{th} day in case of antecedent sensitization(192). Risk factors for NIHRs to heparin are obesity, female gender, old age, pregnancy, and repeated exposures(193,194). If the treatment is continued regardless of a local reaction, the patient may develop generalized eczema or exanthem(195,196). Patients with a NIHR to UFH or LMWH at injection site usually tolerate intravenous administration of UFH (192). Cross-reactivity among LMWHs has been reported in NIHRs (197). However, fondaparinux is generally well-tolerated in patients who react to LMWHs (194). Heparin may induce DRESS (198) and SJS (199).

Immune-mediated heparin-induced thrombocytopenia (HIT) is induced by IgG antibodies against complex of heparin and platelet-factor 4 tetramers (200). HIT manifests as a more than 50% decrease in the platelet count in 5 to 10 days after the onset of treatment (201). The risk of HIT is increased exclusively with UFH (202). Treatment includes the discontinuation of heparin and the introduction of an alternative anticoagulant such as argatroban, fondaparinux, danaparoid, or bivalirudin (203).

The IgE-mediated reactions to heparin manifesting as urticaria, angioedema, and anaphylaxis are rare (197,203,204). Positive STs with UFH and LMWHs have been reported (197,203,204,205)(Table 3). Cross-reactivity in IHRs has been reported between UFH and LMWH and among LMWHs (205).

For IHRs with heparins, diagnostic approach primarily consists of SPTs and IDTs (17). The results of BAT with UFH and LMWH are controversial (204,206,207). Heparin itself may cause a release of histamine, leading to a false positive ST. Further serial dilutions of heparin (1:100, 1:1.000, 1:10.000) might be needed (204). IDTs and PTs with the culprit and alternative heparin are performed in NIHRs (17). PTs, with tape stripping, are less sensitive but may be positive (191)(Table 3).

DPT is considered when the diagnosis is obscure, tissue pathology is unavailable, or an alternative anticoagulant needs to be determined (208). Subcutaneous DPTs with UFC and LMWHs are performed with increasing doses reaching up to a daily dose on the first day, then are evaluated on three consecutive days and day 7 in case of NIHRs. Intravenous DPTs with UFC may also be necessary to prove tolerance for emergency situations both for IHRs and NIHRs (191,192). A standard protocol for UFH desensitization has not been established yet and published as case reports (209,210)(Table 3).

Dipyridamole

Clinical use in COVID-19

Dipyridamole is an inhibitor of phosphodiesterase 3 and 5, thereby itincreases intracellular cAMP and/or cGMP in platelets and inhibits platelet aggregation (211). Besides, it has antiviral features against several viruses (212,213). Dipyridamole as an adjunctive therapy was demonstrated to be associated with decreased D-dimer levels in COVID-19 (214).

Hypersensitivity reactions

DHRs related to dipyridamole are extremely rare. An adult patient with delayed eczematous lesions revealed positive PT results(215). Anaphylaxis or anaphylaxis like reactions were described in two cases however they lack diagnostic tests (216,217)(Table 3).

DIAGNOSIS, DIFFERENTIAL DIAGNOSISAND MANAGEMENT OF DHRs DUE TO DRUGS INVESTIGATED FOR THE TREATMENT OF COVID-19

Considering the severity of the disease and the emergent need for interventions, it is important to give accurate and quick diagnostic and therapeutic decisions in case of DHRs during COVID-19 treatment. However, it is challenging considering the diverse spectrum of drugs introduced either for direct treatment of the disease or other accompanying conditions during the course of the disease especially in severe cases when the disease is prolonged. Consequently,multiple medications applied at a time make a clear-cut association with one medication more difficult.Furthermore, disease-related eruptions as an important reason of differential diagnosis can make the diagnosis even harder, considering that the majority of the drugs used are more associated with drug-related cutaneous NIHRs.

Given the critical state of the disease, the diagnosis can mostly rely on clinical observations without performing *in vivo* tests which have possible contamination risks, and time consuming *in vitro* tests.During a DHR, STs cannot be applied considering the possibility of aggrevation and the low diagnostic accuracy expected during ongoing treatment with antihistamines and corticosteroids. When introducing an alternative drug, a DPT based on established methods may be preferredin order to reduce the risk of a possible DHR (14).

If alternative drugs are not available and underlying DHR is not severe, we can recommend that drugs can be applied with published or tailored desensitization protocols (19,20). When mild, self-limiting DHR is considered, 'treating through' concept, the continued administration of a drug despite a suspected allergic hypersensitivity reaction, can be considered under strict surveillance measures (218). Our recommendations for the diagnosis and management of DHRs due to drugs administered during COVID-19 are listed in Box-1.

CONCLUSION

This review brings together all the published information about DHRs due to current and candidate off-label drugs to treat COVID-19. The current knowledge dependsmostly on previous clinical experience and few published studies or case reports. Hopefully, published literature reveals that most of these drugs rarely cause DHRs but severe reactions may also occur. One limitation of this review is that it includes extremely low number of reports of ADRs seen so far during COVID19 treatment.In near future, we need to obtain data about DHRs during the disease

from ongoing clinical trials and DHR registries.Additionaly as time passes, we will observe if SARS-CoV2 can aggreviate T–cell mediated reactions as some viruses do (219), and if the hyperinflammation observed during the course of the disease may influence DHRs.

This review also highlights the presence of two different groups of disease-related exanthemsas an important cause of differential diagnosis of DHRs expected during the treatment of the disease.We think that it is extremely important to distinguish these disease-related eruptions from true DHR related skin manifestations considering that the majority of the drugs used are more associated with drug-related non-immediate skin reactions.

In near future, further data from ongoing clinical studies and registries established in different countries will enlighten the obscure parts of our understanding on DHRs due to the drugs used in the treatment of COVID-19 and will possibly enable us to establish accurate diagnostic and treatment approaches for these reactions.

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Box 1. Recommendations for diagnosis and management of DHRs in COVID-19

- No equivalent alternatives for the currently off-label repurposed drugs or novel drugs used in COVID-19do exist.
- We should extrapolate our knowledge on DHRs from other clinical situations to COVID-19 considering the scarse experience for the DHRs during the disease.
- Various drugs being used in different phases of the disease seem to cause rare but potentially severe DHRs, mostly non-immediate cutaneous hypersensitivity reactions based on data from limited number of case reports.
- The most important differential diagnosis of these DHRs is disease related exanthems, which can further be classified into the ones similar to those in other viral infections and the others related to thrombovascular events and vascular pathologies seen during COVID-19.
- Experience of diagnostic and management methods for DHRs due to the drugs used in COVID-19 depend mostly on few case reports or series.
- Knowledge of DHRs is urgently needed from pharmacovigilance registries and data from ongoing clinical trials ofCOVID-19.
- Quick diagnostic and therapeutic decisions in case of DHRs during COVID-19 are mandatory.
- Clinical diagnosis of DHRs during COVID-19 might mostly rely on clinical observations and basic laboratory findings regarding the need of urgent treatment of COVID-19.
- If therisks of a DHRoutweighthe benefits obtained from the drug administration, the offending drug should be discontinued.
- When introducing an alternative drug, a DPT may be preferred in order to reduce the risk of a possible DHR.
- If an alternative drug cannot be replaced, the offending drug can be administered via desensitization with published or tailored protocols when there are no contraindications.
- 'Treating through' concept, the continued administration of a drug despite a suspected allergic hypersensitivity reaction, can also be considered under strict surveillance measures if the underlying DHR is mild and self-limiting, and an alternative drug does not exist.

Figure legends

Figure 1. Currently investigated drugs in COVID-19 grouped according to their clinical use

Figure 2. Skin manifestations similar to those in other viral infections. A. Urticaria (23), B. Morbilliform maculopapular exanthem (24), C. Vesiculopapular (chickenpox-like) exanthem (26), D. Intertriginous purpuric rash (30)

Figure 3. Skin manifestations associated with thrombovascular events and vascular pathologies. A. Transient unilateral livedo reticularis (erythema ab igne) (34), B. COVID-19-induced chilblains (35), C. Acro-ischemia with cyanosis, skin bulla, and dry gangrene in critically ill patient (38)

Table 1. Skin manifestations reported associated with COVID-19

Manifestation	Clinical description	Relative frequency*	Similarity to skin rashes of other infections	References
1. Skin manifestations similar to those in other viral infections				
Acute urticaria	Sudden appearance of wheals with a fleeting nature. Continual appearance and disappearance of new lesions is characteristic.	19%	Unspecific for COVID-19; infections are common elicitors for acute urticaria	4,22,23,31
Maculopapular exanthem ("erythematous rash")	Acute erupting, widespread distribution of multiple small, round to oval erythematous macules and/or papules with different degrees of confluence. Mostly trunk, low pruritus.	47%	Unspecific for COVID-19; infections are common elicitors for maculopapular exanthem	4,21,22,24,31,32
Varicella-like exanthem ("chickenpox-like rash")	Monomorphic papulovesicular skin eruption. Erythematous papules and vesicles bilaterally and symmetrically mostly on the trunk.	9%	May be more specific for COVID-19, vesicles are quite uncommon for virus exanthems and more specific for varicella	4,22,25,26
Symmetrical intertriginous exanthem	Flexural erythematous maculopapular exanthem on axillary lesions and trunk +/-antecubal fossae.	Individual case reports	Untypical for infectious exanthems	30
2. Skin manifestations associated with vascular pathologies				
Purpuric exanthem ("purpuric rash")	Skin rash with petechiae.	Individual case reports	Untypical for infectious exanthems,except e.g. Parvovirus B19	22,33
Erythema ab igne	Transient macular	6% together	Untypical for	34

("livedo reticularis")	erythema in a broad reticular pattern on thigh unilaterally.	with cutaneous acroischemia	infectious exanthems	
Chilblain-like lesions	Acute-onset, violaceous, infiltrated and painful plaques on the toes and lateral feet. Vesicles and erosions may be present.	19%	Untypical for infectious exanthems	22, 35,36,37
Cutaneous acro-ischemia	Finger and toe cyanosis, purpura, hematoma, skin bulla and dry gangrene.	6% together with Erythema ab igne ("livedo reticularis")	Typical for severely ill patients with sepsis,	38,39

*Relative frequency in percent of this skin manifestations associated with COVID-19 infections according to Ref 26. In cases, where no numbers are given, only individual case reports do exist.

Drug groups	Drugs	Purpose of use in COVID-19	Hypersensitivity reactions	In vivo tests in IHRs	In vivo tests in NIHRs	In vitro tests for IHRs	In vitro tests for NIHRs	Desensitization
Antiviral drugs	Favipiravir	Viral pneumonia	None					
	Lopinavir/Ritonavir		AGEP[61], MPE[60]					
	Darunavir/Ritonavir		MPE[66] Vesiculobullous lesions[48,64]					DNIHR [66,67]
	Umifenovir (Arbidol)		None					
	Ribavirin		Pruritus[46,55] Eczema[46,53-55] Urticaria[58] MPE[56]		DPT[56]		LTT[57]	DNIHR [58,59]
	Remdesivir (GS-5734)		MPE[51]					
	Oseltamivir		Anaphylaxis[68] SJS/TEN[46], TEN[47]	SPT[68]			LTT[50]	
Immunomodulatory drugs	Azithromycine		MPE[73,74], ACD[75,76], FDE[77] AGEP[78], DRESS[79] SJS[80,81] Anaphylaxis[72] Urticaria[71] Leucocytoclastic vasculitis[82] Hypersensitivity myocarditis[83]	SPT[84,85] IDT[84,85] DPT[87]	PT[75] DPT[87]			DIHR[88]
	Hydroxychloroquine / Chloroquine		MPE[90], AGEP[92,103] DRESS[93-95] Erythema multiforme[96] Bullous erythema[97] SJS/TEN[99,100] Photoallergic dermatitis[101] ACD[102] Anaphylaxis[109,110]	SPT[109]	PT[96,98,103] DPT[90]			DNIHR[104-108] DIHR[109,110]
	Auranofin		None					
	Interferons		Local reaction[116] Urticaria[119,122,123] Eczema[119], FDE[120], MPE[119] Anaphylaxis[124,125]	SPT[122-124] DPT[125]	IDT[119,126] PT[119]			DIHR[123] DNIHR [119,127]

Table 2. Hypersensitivity reactions due to drugs with antiviral properties investigated for the treatment of COVID-19 in clinical trials or in vitro studies

	Nitazoxanide		None					
	Ivermectin		FDE[129], DRESS[130], SJS[131], TEN[132]					

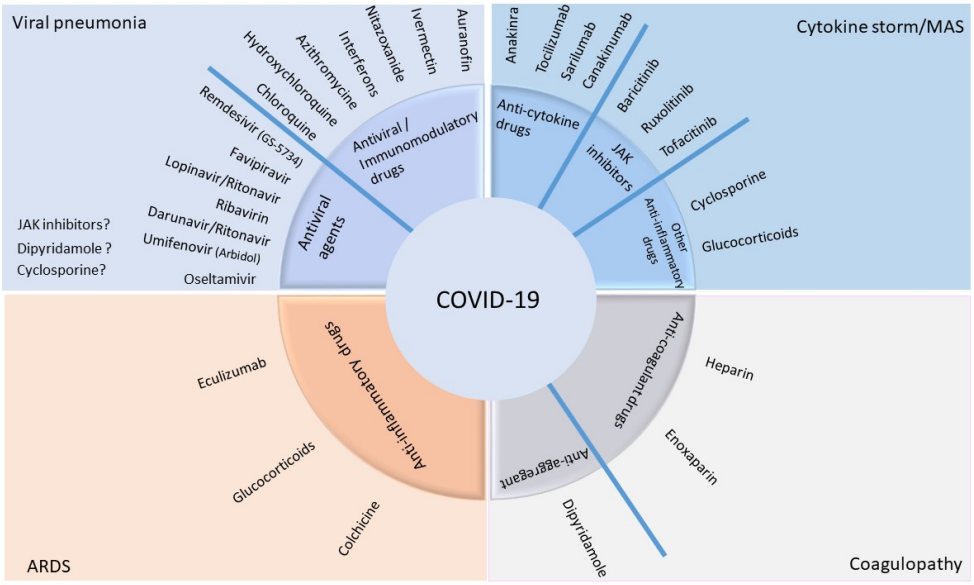
ACD: Acute contact dermatitis; AGEP: Acute generalized exanthematouspustulosis; BAT: Basophil activation test; DIHR: Desensitization for immediate hypersensitivity reactions; DNIHR: Desensitization for non-immediate hypersensitivity reactions; DPT: Drug provocation test; DRESS: Drug related eosinophilia systemic symptoms; FDE: Fixed drug eruption; IDT: Intradermal test; IHR: Immediate hypersensitivity reaction; LTT: Lymphocyte transformation test; MPE: Maculopapular eruption; NIHR: Non-immediate hypersensitivity reaction; PT: Patch test; SJS: Stevens Johnson syndrome; SPT: Skin prick test; ST: Skin test; TEN: Toxic epidermal necrolysis

Table 3. Hypersensitivity reactions due to other drugs investigated for the treatment of COVID-19 related complications in clinical trials or in vitro studies

Drug groups	Drugs	Purpose of use in COVID-19	Hypersensitivity reactions	In vivo tests in IHRs	In vivo tests in NIHRs	In vitro tests for IHRs	Desensitization
Anti-cytokine or anti-inflammatory drugs	Tocilizumab	Cytokine storm/MAS	Papular skin lesions[136] Non-immediate urticaria[141] Anaphylaxis[137,139] DRESS[142,143] AGEP[145], SJS[144]	SPT[137,139] IDT[137,139] DPT[137,139]	IDT[140]		DIHR[134] DNIHR[141]
	Sarilumab		Pruritic rash[155]				
	Anakinra		ISR[147,148] U/Angioedema[149] Anaphylaxis[150,151] Erythematous plaques[152]	SPT[150,151], IDT[150,151]			DIHR[149,151] DNIHR[152]
	Canakinumab		U[137]				
	JAK inhibitors Baricitinib		Palmoplantar pustulosis[160]				
	JAK inhibitors Ruxolitinib		morbiliform rash, exfoliative dermatitis[159]				
	JAK inhibitors Tofacitinib		U[161], palmoplantar pustulosis[162]				
	Cyclosporine		Anaphylaxis[164-167]	SPT[164,166] IDT[164,166]		BAT[166]	

Anti-inflammatory drugs	Glucocorticoids	Cytokine storm/MAS ARDS	IHR[178-183] NIHR[178,179] ACD[179]	ST[178-185] DPT[180-185]	IDT[179,189] PT[179,189] DPT[179,189]	sIgE[181,182] BAT[181,182]	DIHR[186,187]
	Colchicine		Anaphylaxis[151] FDE[168], MPE[169]		DPT[168] PT[170]		DNIHR[169]
	Eculizumab		IHR[172-174] Anaphylaxis[174]	SPT[174], IDT[174]			DIHR[174]
Anti-coagulant or anti-aggregant drugs	Heparin Enoxaparin	Coagulopathy	ISR[192] GDE[195,196] DRESS[198],SJS[199] HIT[200-202] IHR[197,204]	SPT[17] DPT[191,192]	PT[17] DPT[191,192] IDT[17]	BAT[204,206,207]	DIHR[209,210]
	Dipyridamole		Eczema[215] Anaphylaxis[216,217]		PT[215]		

ACD: Acute contact dermatitis; AGEP: Acute generalized exanthematouspustulosis; BAT: Basophil activation n test; DIHR: Desensitization for immediate hypersensitivity reactions; DNIHR: Desensitization for non-immediate hypersensitivity reactions; DPT: Drug provocation test; DRESS: Drug related eosinophilia systemic symptoms; FDE: Fixed drug eruption; HIT: Heparin induced thrombocytopenia; IDT: Intradermal test; IHR: Immediate hypersensitivity reaction; Injection site reaction: ISR; Generalized delayed exanthema: GDE; LTT: Lymphocyte transformation test; MPE: Maculopapular eruption; NIHR: Non-immediate hypersensitivity reaction; PT: Patch test; SJS: Stevens Johnson syndrome; SPT: Skin prick test; ST: Skin test; TEN: Toxic epidermal necrolysis;Urticaria: U



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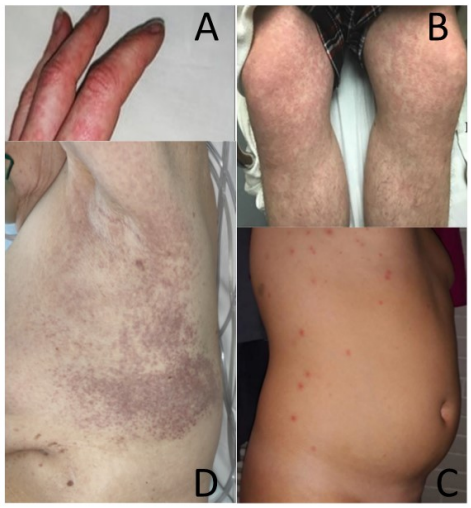

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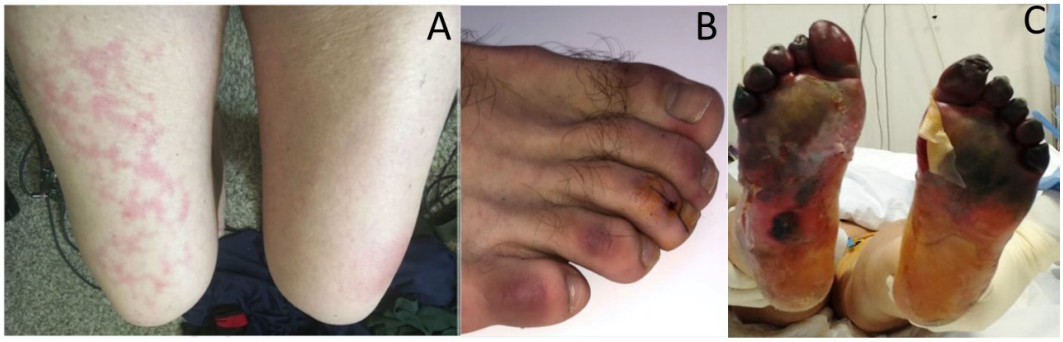

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